Pancreatic cancer: why we must be optimistic?

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Published online: 6 October 2021

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Clinicians and basic scientists struggle to improve the outcome of patients with pancreatic ductal adenocarcinoma (PDA). Late diagnosis limits the benefit of curative loco-regional therapies and places the burden of research on developing better drug therapies. Indeed, most newly diagnosed patients have metastatic disease that is resistant to conventional cytotoxic therapies. The median survival of patients with metastatic PDA remains well under 1 year. Nevertheless, the 5-year survival of PDA improved but remains around 10%. In contrast, there were major advances in other cancers over the past two decades which included targeted therapies and more recently immunotherapy. Sadly, neither of those approaches succeeded in the treatment of PDA, at least for now.

The desperate need for effective systemic therapies in PDA led to numerous clinical trials testing new agents, often by adding them too few of the cytotoxic drug regimens. Unfortunately, trials that in total accrued many thousands of patients did not demonstrate a meaningful clinical benefit for the variety of classes of agents. One major lesson learnt was that targeting a single molecule or pathway without a proof of its importance in driving the PDA was very likely to fail [1]. This was partly because targetable gene mutations or fusions are rare in PDA with possible exception of *KRAS* that is not targetable. The vast majority of trials were done without any target validation in patients with PDA. It became very clear that when it comes to developing new therapies in PDA, its biology must be the driver and that the genotype–phenotype relationship in humans must be firmly established.

Advances in molecular profiling and next-generation sequencing provided limited clinical benefit in treating PDA. One exception is the DNA damage repair defects. *BRCA* and *PLAB2* mutations occur in 5–7% of patients and predict

sensitivity to platinum and PARP inhibitors. Currently these are the major targetable mutations in PDAC. However, more work is needed to expand our ability to exploit DNA repair defects in PDA. Recent work also indicates the presence of targetable mutations in the less than 10% of patients who carry somatic *KRAS* wild-type tumors [2]. This *KRAS* wild-type sub-population represents over 5,000 patients with PDA each year in the USA. Those tumors are enriched with several targetable mutations such as *NRG1*, albeit at a very low frequency. Molecular subtyping using gene expression and transcriptomics is an evolving area of research that resulted in various sub-classifications and signatures that may predict biological behavior [3]. Advanced technologies such as machine learning and network analyses will further advance molecular typing but needs to be coupled with clinical outcome to make it worthwhile. The hope is that future work in coming years will lead to effective therapies that are guided by these advanced technologies largely through personalized therapy.

Optimism for the future is based on the expanding knowledge on PDA's biology coupled by lessons learnt from failed clinical trials. Major reason for optimism is that our understanding of PDA carcinogenesis and progression increased exponentially in the past decade especially in relation to tumor microenvironment. More importantly, there is an expansion of the cadre of researchers who are now focused on PDA. A plethora of experimental therapies at various stages of investigation are under way and many more to come. Active areas include targeting the PDA's stroma and other elements of the microenvironment, modulating immune cells to bolster immunotherapy, taking advantage of the metabolic reprogramming of the cancer cell for selective targeting, targeting nuclear export proteins, and few others. It is expected that with the help of molecular signatures and by identification of active agents, combination therapies will be developed that are patient tailored to also account for the heterogeneity in driver gene mutations [4]. One area of exciting investigation is targeting *KRAS* that is mutated in over 90% of PDAs. However, targeting *KRAS* may prove to be insufficient for sustained disease control in patients

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Fig. 1 New drug development pathway. Drug discovery and pre-clinical testing is shared by academic researchers and pharmaceutical industry. However Phase I to Phase III clinical testing is largely undertaken and sponsored by the pharmaceutical industry. "?" indicates that there is no set pathway to investigate why an experimental drug failed the clinical testing. Academia may need to be engaged in this process for the advancement of science and improvement in new drug development

because it is a very early event in PDA's carcinogenesis, and one must account for the subsequent molecular changes.

Our optimism lies in the advanced knowledge and technology we now have at our disposal, something that is at a much higher level than any time before. One consideration is the weight of evidence we put on pre-clinical models when moving forward. Undoubtedly, models have markedly improved and are indispensable in validating science that supports developing drugs. However, experience shows that they must not be the sole determinant for taking (or not taking) a drug to clinical testing as shown by a recent example in targeting hyaluronan [5]. Critical biology that determines disease behavior and predicts response to a given therapy is best learnt from *in vivo* human investigations and through well-informed clinical trial design [6]. System biology approaches must be considered to decipher critical *in vivo* real-time molecular changes induced by disease progression and or therapy [7] and to understand the non-genetic adaptive drug resistance mechanisms [8]. Such human *in vivo* investigation will vastly benefit from minimally invasive technologies such as radiomics and liquid biopsies. Highly informative proof of concept studies with deep science can be accomplished in relatively small cohorts of patients. Consequently, new drug development becomes a highly interactive and reiterative process whereby continued basic and clinical input guide the data interpretation at each step. Fortunately, most drugs are already out there, but we must learn how to use them correctly based on biology and the uniqueness of each. The pharmaceutical industry owns majority of these assets, and there must be a very close academic/industry collaboration throughout the development process. The most critical decision hubs are transitions from pre-clinical to clinical and from pilot to phase 3 clinical testing. When a clinical trial misses its experimental endpoint, we need to return to the laboratory to investigate the causes of failure to prepare us for the next trial, something we rarely do (Fig. 1).

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